

**REMARKS**

This amendment is supplemental to the amendment and reply filed April 11, 2002, in response to the Office Action dated October 11, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.112 is respectfully requested.

**Submission of a Substitute declaration:**

The declaration was objected to in the Office Action dated October 11, 2001, because corrections were made that were not signed and dated. **A substitute declaration is attached hereto.**

**Amendment of the Text of the Specification:**

The application is amended as set forth above. In accordance with the rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a marked up version of the claims showing all amendments is attached hereto as an appendix.

The text of the specification is amended by changing the word "capable" to "incapable" at page 21, line 3. The original text stated that, for embodiments in which a human genome is transferred into a recipient oocyte, the genome "may be modified such that the cell is capable of producing a viable embryo." The amendment corrects a typographical error in the original specification, as is evident from the text that follows the corrected statement, which describes implementing the modification by introducing a genetic modification that would prevent the embryo from attaching or developing in the uterus (see page 21, lines 4-9). Another typographical error in the same paragraph is corrected by amending the word "affected" at page 21, line 5, to "effected." No new matter is added by these amendments.

**Amendment of the Claims:**

Original claims 1, 2, 4-16, and 19-68 are canceled and new claims 69-231 are submitted. The new claims are directed to the subject matter of elected claims 1-39 that were examined and addressed in the Office Action dated October 11, 2001.

**Support for the New Claims in the Specification and in the Original Claims:**

The new independent claims all recite the use of mammalian cells, and are limited to the preferred embodiment of the invention in which the donor cells are senescent or near senescence. Use of donor cells that are senescent or near senescence is described, for example, at page 16, lines 1-2, of the specification.

New independent claim 69 and dependent claims 70-94 are directed to a method for producing a rejuvenated cell comprising transferring the genome of a donor cell into a recipient mammalian oocyte, generating an embryo, and then a teratoma, and isolating a rejuvenated mammalian cell from the teratoma, support for which is found, for example, at page 17, line 17, to page 18, line 6, at page 20, line 13, to page 21, line 1, and in original claims 1 and 8.

New independent claim 93 and dependent claims 94-112 are directed to a general method for producing a rejuvenated cell by transfer of the genome of a donor cell into a recipient mammalian oocyte to generate an embryo, and generating and isolating a rejuvenated cell from said embryo, support for which is found, for example, at page 2, lines 3-14; in the paragraph bridging pages 9-10, and in original claims 37-39.

New independent claim 113 and dependent claims 114-127 are directed to a method for producing a cloned mammal comprising rejuvenated cells, support for which is found in original claims 25-28.

New independent claim 118 and dependent claims 129-150 are directed to a method for producing a genetically altered rejuvenated cell comprising modifying the genome of the donor cell prior to nuclear transfer, support for which is found, for example, at page 23, lines 11-14, and in original claims 21 and 22.

New independent claim 151 and dependent claims 152-169 are directed to a method for producing a genetically altered rejuvenated cell comprising modifying the genome of a rejuvenated cell produced by the disclosed nuclear transfer technique, support for which is also found, for example, at page 23, lines 17-20, and in original claims 21 and 22.

New claims 204-231 are directed to rejuvenated cells, and tissues, and non-human mammals comprising such rejuvenated cells and tissues, support for which is found, for example at page 21, lines 14-17; page 22, lines 3-6 and 15-17; and in original claims 15 and 16.

Support for reciting a mammalian primary cell as the genomic donor cell is found in the specification, for example, at page 15, lines 15-18, where primary cells are defined, and at lines 1-3 of page 16, which describes using senescent or near-senescent primary cells as donor cells in a preferred embodiment of the invention.

Support for reciting generating and isolating a "rejuvenated cell" is found in the specification at page 15, lines 18-20, which describes a rejuvenated cell as a cell having an increased proliferative life-span and lengthened telomeres, and in Example 2, which describes producing rejuvenated cells having increased EPC-1 activity increased EPC-1

telomerase activity, and telomeres lengthened from the lengths found in the primary donor cell to at be least as long as the telomeres found in an age-matched control cell (pages 32-34).

The method wherein the donor cell and the isolated rejuvenated cell are either of the same or of different cell types, as recited in new claims 72 and 73, is described, for example, in original claims 1 and 8.

Growing the rejuvenated cell in the presence of growth factors to facilitate further differentiation as recited in new claim 74 is supported, for example, at page 21, lines 16-19, and in original claim 13.

Isolating a differentiated rejuvenated cell of a cell type recited in new claim 75 is supported, for example, at page 21, line 16, to page 22, line 6, and in original claim 11.

Use of the cell types recited in new claim 77 as a donor cell is supported, for example, at page 18, lines 15-18; and obtaining the donor cell from an organ recited in new claim 78 is supported, for example, at page 18, line 19.

The method wherein the step of generating the rejuvenated cell from the embryo comprises isolating a rejuvenated blastocyst, embryonic disc cell, inner cell mass cell, embryonic stem cell, or a teratoma cell, as recited in new claim 94, is disclosed, for example, at lines 7-9 of page 18.

Generating an isolated rejuvenated cell that is an embryonic stem cell, as recited in new claim 95, is supported, for example, in the paragraph bridging pages 9 and 10, and in original claims 1 and 39; and differentiation of the rejuvenated stem cell into a one of the cell types recited in new claim 96 is supported, for example, in the paragraph bridging pages 21 and 22, and in original claim 11.

Generating a tissue comprising rejuvenated mammalian cells as recited in new claim 98 is supported, for example, at lines 10-15 of page 21.

Obtaining a rejuvenated cell from a fetal or developed non-human mammal produced by nuclear transfer as recited in new claims 106-112 is supported, for example, at page 22, line 15, to page 24, line 16.

Practicing the invention using a donor cell that is of a different species than the recipient oocyte, as recited in new claim 106, is supported, for example, and in original claim 38.

Using a donor cell that is either passaged or induced into a state of senescence or near senescence, as recited in new claims 101 and 102, is supported, for example, by original claims 21 and 22.

Characterizing the rejuvenated cells produced by the invention as having lengthened telomeres as recited in new claims 186 and 187, as having lengthened proliferative life-span as recited in new claim 188, and as having increased EPC-1 and telomerase activities as recited in new claims 189 and 190, is supported, for example by the experimental results disclosed in Examples 2 and 3 on pages 29-38.

Practicing the invention by effecting multiple genetic alterations in the genome of a rejuvenated cell, as recited in new claim 130, is supported, for example, in original claim 21.

Obtaining a rejuvenated genetically modified cell from a fetal or developed genetically modified non-human mammal produced by nuclear transfer as recited in new claims 132-134 is supported, for example, at in the paragraph bridging pages 22-23, and in original claims 25-28.

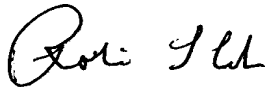
Generating a re-cloned, rejuvenated, cell having multiple genetic modifications as recited in new claims 135-137 is supported, for example, at page 23, line 7, to page 24, line 16; and by original claim 29.

No new matter has been introduced by the amendment.

The issues raised by the Office Action dated October 11, 2001, were addressed in the Amendment and Reply filed April 11, 2002. The new claims incorporate the changes in the claims made in response to issues raised in the Office Action dated October 11, 2001.

Applicants respectfully submit that a Notice of Allowance is next in order. If the Examiner has any further questions or issues to raise regarding the subject application, it is respectfully requested that she contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,



Robin L. Teskin

Date: May 28, 2002

Registration No. 35,030

**APPENDIX**

The following marked-up versions of paragraphs of the specification amended as described above, showing the changes that are made thereto, are provided in accordance with the rules for amending applications set forth in 37 CFR 1.121.

**IN THE SPECIFICATION:**

Please substitute the paragraph beginning at line 2 of page 21 with the following amended paragraph:

- - In embodiments wherein the donor cell, nucleus or chromosomes are human, the genome of the primary cell may be modified such that the cell is [capable] incapable of producing a viable embryo. This may be [affected] effected by inactivating or knocking out one or more genes required for the formation of one of the three germ layers, or by expressing a "suicide" gene from a developmentally regulated promoter specifically expressed in a cell type contained in a germ layer which is not of interest. Alternatively, gene knockouts or suicide gene expression could be targeted to genes specifically required for attachment to or development in a mammalian uterus. - -